REMARKS/ARGUMENTS

Reconsideration and continued examination of the above-identified application are respectfully requested.

Claims 26-42 and 44-51 are pending. Claims 27-32, 35, 36, 39-41, and 44-51 are withdrawn from further consideration as being drawn to non-elected inventions. Claims 26, 33, 34, 37, 38, and 42 are currently under examination. By way of this amendment, claim 26 has been amended to recite that the agent inhibits the expression of the Asef by the RNA interference on the expression of the gene or by antisense inhibition on the expression of the gene. Full support for this amendment can be found in the claims as originally filed, such as claim 33, as well as the present application, for instance, at paragraphs [0048] and [0049]. Further, claim 38 has been amended to recite a pharmaceutical composition which contains the oligonucleotide of claim 37 and a pharmaceutical carrier. Support for this amendment can be found, for instance, in the present application at paragraphs [0055] to [0063]. Also, claims 37 and 42 have been amended to recite that the oligonucleotide consists of the nucleotide sequence set forth in the recited claims. Accordingly, no questions of new matter should arise and entry of the amendment is respectfully requested.

Claim Objection under 37 C.F.R. §1.75(c)

At page 4 of the Office Action, the Examiner rejects claim 38 under 35 U.S.C. §1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. This objection is respectfully traversed.

Claim 38 has been amended as described above, such that this objection should be withdrawn.

Rejection of Claim 26 under 35 U.S.C. §112, first paragraph

At pages 5-6 of the Office Action, the Examiner rejects claim 26, under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner asserts that the claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

The Examiner indicated that the present specification provides a sufficient disclosure for "shRNA-Asef" agents that inhibit the expression of the Asef gene. The specification enables and discloses RNA interference of the Asef gene in general. Further, for instance, paragraphs [0048] and [0049] describe an agent that inhibits the expression of the Asef gene by the RNA interference on the expression of the gene or by antisense inhibition on the expression of the gene. Specific examples are also provided in the present application. Further, the present invention describes dosage ranges and pharmaceutical compositions that can contain the agent, see, for instance, paragraphs [0055] - [0063]. Further, the examples of the present application clearly show and enable the inhibition of the expression of the Asef gene. Accordingly, claim 26, as amended, is clearly described and satisfies all paragraphs of 35 U.S.C. §112. For these reasons, this rejection should be withdrawn.

Rejection of Claims 26, 33, and 34 under 35 U.S.C. §102(a) -- Jimbo et al.

At pages 6-7 of the Office Action, the Examiner rejects claims 26 and 33-34 under 35 U.S.C. §102(a) as being anticipated by Jimbo et al. (MOLECULAR MEDICINE, 2002). The rejection is respectfully traversed.

The applicants note that Jimbo et al. is the work of the present inventors, and the publication date of the reference is October 25, 2002. Attached is an English translation of the cover page of the journal to further confirm the publication date.

Since the reference relied upon by the Examiner in this §102(a) rejection is the work of the present inventors, the reference would not be prior art under 35 U.S.C. §102(a) since it is not by "another." In particular, the applicants are preparing a submission under 37 C.F.R. §1.132 to state that the reference relied upon by the Examiner discloses subject matter derived from the applicants. In particular, as explained in the Declaration to be submitted shortly, the listed authors of the Jimbo et al. reference are Tetsu Akiyama, Yoshihiro Kawasaki, and Takeshi Jimbo, while the actual inventors of the present invention are Tetsu Akiyama, Yoshihiro Kawasaki, and Rina Satoh. Takeshi Jimbo is a research assistant working under the inventors and was not an inventor, but contributed to the preparation of the article for publication purposes. This is the reason why the listed authors of the reference and inventors of the present application differ.

Accordingly, this rejection should be withdrawn.

Rejection of Claims 26, 33, and 34 under 35 U.S.C. §102(a) -- Akiyama et al.

At page 7 of the Office Action, the Examiner rejects claims 26 and 33-34 under 35 U.S.C. §102(a) as being anticipated by Akiyama (JOURNAL OF CLINICAL AND EXPERIMENTAL MEDICINE, 2003). This rejection is respectfully traversed.

The Akiyama reference has a publication date of June 28, 2003, whereas the present application is based upon a PCT application, which claims a Japanese priority date of November 24, 2002. Submitted with this response is a certified English translation of the Japanese priority application from which the current application claims priority. As can be seen, the claims, as

pending, are fully supported in this Japanese priority document and, therefore, Akiyama et al. would not be prior art to the claimed invention. For this reason, this rejection should be withdrawn.

Rejection of Claims 26, 37-38, and 42 under 35 U.S.C. §102(a) or (e) -- Drmanac et al.

At pages 7-9 of the Office Action, the Examiner rejects claims 26, 37-38, and 42 under 35 U.S.C. §102(a) or (e) as being anticipated by Drmanac et al. (US Patent Application Publication No. 2003/0073623 A1). The Examiner asserts that Drmanac et al. relates to an isolated polynucleotide that comprises present SEQ ID NO:1. The Examiner also asserts that the document further describes that the isolated polynucleotide, or fragments thereof, can be used in the generation of antisense DNA or RNA. It is therefore the opinion of the Examiner that all of the limitations of the present claims are anticipated by Drmanac et al. This rejection is respectfully traversed.

With regard to claim 37, the claimed invention is not anticipated by Drmanac et al. since Drmanac et al. does not teach an oligonucleotide consisting of SEQ ID NO: 1. With respect to claim 26, Drmanac et al. relates to a large number of EST including the sequence set forth in SEQ ID NO: 1044. In the reference, Drmamac et al. shows examples of the use of the DNA fragments, such as for generating antisense DNA or RNA, but the examples are merely some general aspects of uses and there is no enabling description for the use of the disclosed DNA fragments. As the Examiner states, the reference allegedly states that the fragments of SEQ ID NO: 1044 can be used in the generation of antisense DNA or RNA, and that the fragments of SEQ ID NO: 1044 can be used to control the gene expression through a triple helix formation or antisense DNA or RNA that binds to an mRNA sequence thereby blocking translation of the mRNA molecule. However, there is no specific enabling teaching in the reference that the sequence set forth in SEQ ID NO: 1044 actually provides effective antisense DNAs or RNAs. Moreover, there is no enabling teaching in the cited

reference that metastasis of a colorectal cancer is inhibited by inhibiting expression of Asef gene using the sequence set forth in SEQ ID NO: 1044, which indicates that the Drmanac et al. reference does not teach the subject matter of the invention claimed in the amended claim 26 of the present invention. In addition, the optimal length of a DNA fragment to show an RNA interference effect is about 21 mer. Further, it is known that a DNA fragment consisting of a nucleotide sequence of 35 mer or more exhibits a nonspecific effect and loses the characteristic effect of RNAi to specifically degrade a target mRNA only. Although the sequence set forth in SEQ ID NO: 1044 consisting of 459 nucleotides is a partial sequence of the Asef gene as shown in the attached search results (i), (ii), and (iii), a DNA consisting of the sequence of SEQ ID NO: 1044 would now show an Asef specific RNAi effect due it its extremely long length, which is larger than the optimal length of RNAi. On the other hand, an oligonucleotide consisting of the nucleotide sequence, for instance, as set forth in SEQ ID NO: 1 of the present invention, is a partial sequence of the Asef gene as shown on the attached search result (iv) and provides an Asef specific RNAi effect.

In view of the reasons above, the applicants believe that the Drmanac et al. reference does not teach the invention claimed in the amended claims 26, 37-38, and 42, and therefore amended claims are not anticipated by the Drmanac et al. reference.

Rejection of Claims 26, 33, 34, 37, 38, and 42 under 35 U.S.C. §103(a) -- Kawasaki et al. in view of Fire et al. and Costa et al.

At pages 10-12 of the Office Action, the Examiner rejects claims 26, 33-34, 37-38, and 42 under 35 U.S.C. §103(a) as being un-patentable over Kawasaki et al., further in view of Fire et al. (U.S. Patent No. 6,506,559 B1) and Costa et al. (US Patent Application Publication No. 2003/0157531 A1). The Examiner in the Office Action states that Kawasaki et al. is relied upon as before, but the Examiner is incorrect. Kawasaki et al. was not cited in any previous prior art

Clarification is respectfully requested.

The Examiner argues that it would have been obvious to one skilled in the art, at the time the instantly claimed invention was made, to make an siRNA oligonucleotide targeting the Asef gene sequence in order to inhibit the expression of the Asef gene *in vitro*. The Examiner asserted that one of ordinary skill in the art would have been sufficiently motivated to inhibit the expression of Asef by targeting its cDNA sequence of Kawasaki et al. since it was an art-recognized goal to inhibit the expression of a gene implicated in colorectal cancer metastasis in vitro as taught by Costa et al., and also because Kawasaki et al. explicitly teaches that Asef is expressed in colorectal epithelial cells and interacts with APC (a gene mutated in colorectal cancer as taught by Kawasaki et al., pages 1194-1195). This rejection is respectfully traversed.

The Examiner seems to be referring to the SCIENCE article, Vol. 289, pp. 1194-1197, 2000, as the Kawasaki reference. This SCIENCE article states that Asef relates to a morphology and migration of cells, but never teaches or suggests that Asef relates to metastasis of colorectal cancer. Meanwhile, Senda et al. demonstrated in JPN. J. CLIN. ELECTRON MICROSC., Vol. 33, pp. 65-74, 2001, that, "It is a future task to explore how the cytoskeleton-mediated effect of APC on cell motility associates with the tumor suppressor function thereof." APC gene is involved in development of colorectal. Please see the third paragraph of the partial translation of JPN. J. CLIN. ELECTRON MICROSC., Vol. 33, pp. 65-74, 2001, that has already been filed with the U.S. Patent and Trademark Office, along with an Information Disclosure Statement. In view of Senda et al., the applicants believe that one of ordinary skill in the art, at the time the instantly claimed invention was made, was on a technical level where it can be said that a molecule relating to cell motility would be particular in the metastasis of colorectal cancer. Thus, the subject matter of the amended claims 26, 33-34, 37-38, and 42, namely achieving inhibition of metastasis of a colorectal cancer by inhibiting

expression of Asef gnee, was first invented by the present inventors who have produced dominant negative mutants of Asef, shRNA against Asef, and the like, and have demonstrated using these mutants and shRNA, in a metastasis model of colorectal cancer, and that metastasis of a colorectal cancer was inhibited by inhibiting the expression of Asef gene.

The Costa et al. reference relates to a double-stranded RNA targeting to TAO/JNK kinase that is a factor involved in β-catenin signaling pathway, and which inhibited growth of a colorectal cancer cell line. However, the Costa et al. reference shows no data and no evidence that indicates that all of the considerable number of molecules involved in β-catenin signaling pathway can be targets of inhibition of colorectal cancer metastasis, and further, it never teaches or suggests that Asef gene can be a suitable target among the considerable number of molecules.

The Fire et al. reference relates to general RNAi techniques, and never teaches or suggests that Asef gene is involved in colorectal cancer metastasis.

Therefore, the applicants believe that the subject matter of amended claims 26, 33-34, 37-38, and 42, namely achieving inhibition of metastasis of a colorectal cancer by inhibiting expression of Asef gene, would not have been obvious to one of ordinary skill in the art, at the time the claimed invention was made, even if it was able to refer to the Kawasaki et al. reference and further to the references of Costa et al. and Fire et al. at that time. The rejection should be withdrawn.

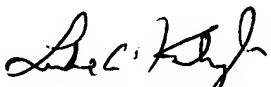
CONCLUSION

In view of the foregoing remarks, the applicant respectfully requests the reconsideration of this application and the timely allowance of the pending claims.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0925. If a fee is required for an extension of time under 37 C.F.R. §

1.136 not accounted for above, such extension is requested and should also be charged to said Deposit Account.

Respectfully submitted,



Luke A. Kilyk
Reg. No. 33,251

Atty. Docket No. 3190-078
KILYK & BOWERSOX, P.L.L.C.
400 Holiday Court, Suite 102
Warrenton, VA 20186
Tel.: (540) 428-1701
Fax: (540) 428-1720

Attachments: Copy of cover page of the journal that contains the Jimbo et al. reference and a partial translation thereof.
English translation of Japanese Patent Application No. JP2002-382083
Search Results:
(i) NM_032995 (Asef gene)
(ii) PSIPS View Sequence: 1044 for 20030073623
(iii) Blast 2 Sequences result for SEQ ID NO: 1044 of the Drmanac et al. reference and Asef gene
(iv) Blast 2 Sequences results for SEQ ID NO: 1 of the present invention and Asef gene